

**REMARKS**

This supplemental amendment and response is submitted to correct an omission in the Amendment and Response filed on October 25, 2006.

**I. Substance of Telephonic Interview**

Applicants gratefully acknowledge Examiner's willingness to conduct a telephonic interview on October 20, 2006. Applicants' attorney presented proposed amendments to the claims for discussion and sought clarification regarding a citation to the Stolowitz reference in the Examiner's earlier Office Actions. Examiner's comments clarifying the pending issues under 35 USC §§ 112, 102 and 103 are much appreciated. In addition, Examiner graciously admitted previous arguments presented on: (1) page 21 lines 6-12; (2) page 27 lines 1-6; and (3) page 32 lines 17-22 of the Office Action, contained a typo ("e.g., see Stolowitz, column 6, lines 43-56, "An 'affinity ligand' ... may also be used as a diagnostic reagent ...[which] permits the detection and/or quantitation of such biological molecules"; see also lines 23-26"). Since no such citation exists in the Stolowitz reference, the accompanying arguments in those portions of the Office Action are rendered moot.

**II. Status Of The Claims.**

Claims 1, 2, 4-13, 15, 18, 20-25, 27, 29, and 32-34 and 37 are pending in the Application. This Response and Amendment amends Claims 1, 12, 25 and 29; cancels Claims 2, 4, 13, 15, 20-24, 27 and 37; and adds new claim 38.

**III. Claim Amendments And New Claims.**

The claim amendments and new claims are described below. Applicants respectfully submit that these claim amendments and new claims do not add new matter. Moreover the amendments cancel claims and the amendments to claim 1, 12 and 29 comply with requirements of form expressly set forth in a previous Office action. In addition, the amendments are believed to place the claims in condition for allowance or in better form for consideration on appeal. Accordingly entry of the claim amendments and new claims is respectfully requested.

**A. Claims 1, 12, 25 and 29.**

Claims 1, 12 and 29 have been amended to incorporate the limitations of canceled

claims 4 and 15. Claim 25 is amended to change the dependency from a canceled claim to claim 1. Accordingly, the amendment to the claims does not add new matter.

#### B. Claim 38

New claim 38 is added to provide an independent claim for a particularly preferred embodiment of the invention, wherein 1,2,4-carbonyl di-triazole is used as an activating compound and the immobilized biomolecule is an oligonucleotide. Support for the new claim can be found throughout the specification, as well as canceled claims 4 and 15 and pending claims 25 and 33. Accordingly, this new claim does not add new matter.

#### IV. The 35 USC § 112 Rejections

Claims 1, 2, 4-13, 15, 18, 29, 32-34 and 37 are rejected under 35 USC 112, second paragraph for being indefinite. Claims 1, 12 and 29 are amended to replace the term “consisting essentially of an organic polymer” with “the solid support being formed from a material selected from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon” to obviate the rejection.

Claims 1, 2, 4-13, 15, 18, 29, 32-34 and 37 are rejected under 35 USC 112, first paragraph for containing new matter. Claims 1, 12 and 29 are amended to replace the term “consisting essentially of an organic polymer” with “the solid support being formed from a material selected from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon” to obviate the rejection.

#### V. The 35 USC § 102 Rejection.

The Office has rejected Claims 1, 2, 9, 12, 13, 18, 29 and 32 under 35 U.S.C. § 102(b) as being anticipated by Jennison et al., (Jennison et al., “Biocoating of Implants with Mediator Molecules: Surface Enhancement of Metals by Treatment with Chromosulfuric Acid: Mat.-wiss. U. Werkstofftech. 1999, 30, 838-845) for the reasons stated in numbered paragraphs 5 and 6 of the Office Action.

Step (a) of independent Claims 1, 12 and 29 is limited to “the solid support being formed from a material selected from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate and nylon”. Jennison et al. do not disclose a solid support as set forth in Claims 1, 12 and 29. In addition, Jennison et al. do not teach or suggest forming an activated support, “wherein the activating compound is

1,2,4-carbonyl di-triazole" nor "reacting the biological molecule with the 1,2,4-carbonyl di-triazole activated support ."

Accordingly, Applicants request withdrawal of the Rejection under 35 U.S.C. § 102(b) on this basis.

## **VI. The 35 USC § 103 Rejections.**

### **A. The Invention Is Non-Obvious Over Jennison et al. and Stolowitz.**

Claims 1,2, 4, 9-13, 15, 18, 29 and 32 are rejected under 35 U.S.C. § 103(a) as unpatentable over Jennison et al., (Jennison et al., "Biocoating of Implants with Mediator Molecules: Surface Enhancement of Metals by Treatment with Chromosulfuric Acid: Mat.-wiss. U. Werkstofftech. 1999, 30, 838-845) and Stolowitz et al. (WO 87/06586) for the reasons stated in numbered paragraphs 7 and 8 of the Office Action.

As set forth for the 35 USC 102(b) rejection above, Jennison et al. does not teach all the limitations of amended claims 1, 2, 9, 12, 13, 18, 29 and 32 and does not thereby render the claimed invention obvious.

Stolowitz et al. fails to cure the deficiencies of Jennison et al. Although Examiner states:

A person of skill in the art would have reasonably expected to be successful because Stolowitz et al. show the use of 1,2,4-carbonyl di-triazole in a coupling reaction involving aminopropyl silica gel ... which is exactly the same reaction disclosed by Jennison et al.

the claimed invention is limited to solid supports "formed from a material selected from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate and nylon" not aminopropyl silica gel.

Applicants respectfully submit neither Jennison et al. nor Stolowitz teach or suggest "providing a solid support, the solid support being formed from a material selected from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon as set forth in step (a) of the claimed invention. As a consequence neither reference teaches or suggests "reacting the available amino group on [a] solid support...formed from a material selected from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon with ...1,2,4-carbonyl di-triazole." Likewise, neither reference teaches or suggests "reacting

[a] biological molecule with [a] 1,2,4-carbonyl di-triazole activated support” ...” formed from a material selected from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon” as claimed by applicants. Consequently, the combined teachings Jennison and Stolowitz fail to teach or suggest all the claim limitations

Moreover, Applicants respectfully submit Stolowitz et al.’s broad teaching that they obtain “near quantitative derivatization of bonded supports .... by this synthetic route” and that their method is “versatile” because “almost [an] infinite variety of ligands ...can be employed as functionalizing reagents” provides nothing more than an “obvious to try” rationale, where “what would have been ‘obvious to try’ would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful....” In re O’Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Here, the “parameters” and “possible choices” are not limited to a choice of six azolides, as suggested by the Examiner, but also includes a plethora of “bonded supports” and an “infinite variety of ligands,” which react with the azolides.

Applicants respectfully request withdrawal of the rejection on the basis that Jennison et al. and Stolowitz et al. do not teach or suggest all the limitations of the claimed invention.

#### **B. The Invention Is Non-Obvious Over Jennison, Stolowitz, Milton, Okamoto, and Guo.**

Claims 1, 2, 4-13, 15, 18, 20-25, 27, 29 and 32-34 are rejected under 35 U.S.C. § 103(a) as unpatentable over Jennison et al., (Jennison et al., “Biocoating of Implants with Mediator Molecules: Surface Enhancement of Metals by Treatment with Chromosulfuric Acid; Mat.-wiss. U. Werkstofftech. 1999, 30, 838-845) and Stolowitz et al. (WO 87/06586) and Milton (US 6,146,833) and Okamoto et al. (US 6,476,215) and Guo et al. (Nuc. Acids Res. 1994, pp. 5456-5465) for the reasons stated in numbered paragraph 9 and 10 of the Office Action.

As set forth above for the 35 USC 103(a) rejection above, Jennison et al. and Stolowitz et al. do not teach all the limitations of amended claims 1, 2, 4, 9-13, 15, 18,

21, 29, 32 and 37 and thus do not render the claimed invention obvious. Moreover, Examiner admits Jennison et al. and Stolowitz et al. fail to recite a solid support selected from the group consisting of cellulose, agarose, polypropylene, polymethacrylate and nylon.

Examiner cites the combined references of Milton Okamoto et al. and Guo et al. in an attempt to remedy this deficiency. Neither Okamoto et al. nor Guo et al. teach or suggest “providing a solid support having at least one available amino group, the solid support being formed from a material selected from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon.” Therefore, the Milton reference is the only cited reference that discloses one member of the Markush group, namely “aminated” polypropylene.

Applicants respectfully submit Examiner has not provided the requisite motivation to pick and choose the biological molecule immobilization method of Jennison et al., modified by substituting the CDT activating compound of Stolowitz et al., the combination further modified by substituting the aminated polypropylene of Milton as the solid support. Instead, the Office merely asserts the disclosure of “aminated polypropylene” by Milton. (See, e.g., paragraph [7] on page 29 of the Office Action).

Further, in order to render the present claims obvious, there must be something in the prior art to suggest not only the desirability of combining the references, but a suggestion that they be combined in the particular manner and configuration as the claimed invention. *Uniroyal, Inc. v. Rudkin Wiley Corp.* 837 F.2d 1044, 1051, 5 USPQ 2d 1434 (Fed. Cir. 1988), cert. denied, 488 U.S. 825 (1988). The Patent and Trademark Office has not identified any such suggestion.

For example, the procedure for immobilizing biopolymers disclosed in Milton includes reacting the acyl fluoride functionality on the substrate with a biopolymer. In contrast, Applicants’ claimed method reacts the biological molecule with a 1,2,4-carbonyl di-triazole activated support. Likewise, Milton et al.’s teaching that “any protein or peptide with surface amino groups, e.g., lysine can be immobilized to a solid support having pendant acyl fluoride functionalities (column 4, lines 28-30, emphasis added) does not teach or suggest reacting a biological molecule with a CDT activated support.

Finally, the combined teachings Jennison, Stolowitz, Milton, Okamoto, and Guo fail to teach or suggest all the claim limitations. None of the cited references teach or suggest “reacting the available amino group on [a] solid support...formed from a material selected from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon with ...1,2,4-carbonyl di-triazole.” Likewise, none of the cited references teach or suggest “reacting [a] biological molecule with [a] 1,2,4-carbonyl di-triazole activated support” ...” formed from a material selected from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon” as claimed by applicants.

Applicants request withdrawal of the rejection and allowance of all pending claims as the combination of Jennison, Stolowitz, Milton, Okamoto and Guo fail to teach or suggest all the claim limitations.

### C. Applicant's Invention Exhibits Significant And Unexpected Results Over The Prior Art.

Applicants submit that, insofar as the claims may be *prima facie* obvious (which is denied), any such *prima facie* case is rebutted by the evidence of the superior and unexpected results of Applicants' claimed method using 1,2,4-carbonyl di-triazole, as set forth in claims 1, 12, 29 and 38, for attaching a biological molecule.

It is well-settled law that a *prima facie* case of obviousness under 35 U.S.C. § 103 can be rebutted by evidence that the claimed invention provides unexpected advantages, and that evidence provided by the specification itself must be considered. The experimental results set out in the specification provide evidence that the claimed invention provides unexpected advantages for attaching a biological molecule. In particular, the test results summarized in Examples 2 and 3 of the Specification are evidence of the remarkable ability of the claimed invention to attach a biological molecule, exhibiting increased oligonucleotide loading and higher sensitivity for analyte detection than the prior art acyl fluoride (AcF) method, an example of the method disclosed in Milton, and a CDI method, as taught by Hermanson et al.

Applicant respectfully disagrees with Examiner's contention that Applicants failed to provide a comparison with the closest prior art of record. The Jennison et al. reference is presently the closest prior art of record, being cited for anticipating the

claimed invention under 35 USC § 102. Applicants results compare the attachment of a biological molecule to a solid support using a CDI method, as does Jennison et al.

Alternatively, the Milton reference provides closer prior art than the Stolowitz et al. reference since Milton provides a method of attaching a biological molecule to a solid support using an acyl fluoride. The Stolowitz et al. reference is not the closest art of record because the reference teaches different solid supports and different ligands than the biological molecules of the claimed invention.

In essence, Examiner's requirement that Applicants provide a comparison with the N,N'-carbonyl di-1,2,3-triazole of Stolowitz is asking the Applicant's to compare the claimed invention with an idealized version of Stolowitz that does not exist.

Although evidence of unexpected results must compare the claimed invention with the closest prior art, applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art. *In re Geiger*, 815 F.2d 686, 689, 2 USPQ2d 1276, 1279 (Fed. Cir. 1987)

See, also, *In re Chapman*, 357 F.2d 418, 148 USPQ 711 (CCPA 1966) (Requiring applicant to compare claimed invention with polymer suggested by the combination of references relied upon in the rejection of the claimed invention under 35 U.S.C. 103 "would be requiring comparison of the results of the invention with the results of the invention." 357 F.2d at 422, 148 USPQ at 714.)

Here, the Examiner seems to expect Applicants to modify Stolowitz by substituting a different solid support, e.g., aminated polypropylene, and a biological molecule in place of a "ligand" or "functionalizing reagent" so that a comparison can be made using CDT. However, the closest prior art is either Jennison et al. or Milton, not the combination of references relied on for the rejection of the claimed invention under 35 USC §103.

To summarize Applicants unexpected results, when fluorescently labeled amino-oligonucleotides were attached to aminated polypropylene using the AcF method of Milton , a CDI method like Jennison et al. or the CDT method of the claimed invention, Applicants CDT method provided brighter fluorescent spots, corresponding to higher loading of oligonucleotides on the solid support, at each concentration level compared to the other two methods. The higher loading of oligonucleotides demonstrated in Example 2 was shown to have a statistical and practical effect on the assays described in Example 3. Spots (brightness captured by CCD camera) detecting an analyte started as low as 1

pg/ml, and increased in brightness as the concentration increased to 1000 pg/ml. In contrast, the CDI method did not begin to show any spots until about 25 pg/ml. Thus, based on a side to side comparison of CDI and CDT mediated attachment of biological molecules, the present invention unexpectedly improved the sensitivity of an assay ten to twenty-five fold.

Applicants submit that insofar as it may be *prima facie* obvious to modify or combine Jennison , Stolowitz, Milton, Okamoto and Guo, the use 1,2,4-carbonyl di-triazole as set forth in claims 1, 12, 29 and 38, provides unexpected advantages over and above a mere equivalence of coupling reagents. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. § 103 and allowance of claims 4, 15 and 37.

#### D. The Invention Is Non-Obvious Over Abbott et al. and Haginiaka et al.

Claims 1,2, 4, 9-13, 15, 18, 29 and 32 are rejected under 35 U.S.C. § 103(a) as unpatentable over Abbott et al., (US Patent Application No 2002/0055093 A1) in view of Haginiaka et al. (Haginiaka et al. "Retention and enantioselectivity of 2-arylpropionic acid derivatives on an avidin-bonded silica column: Influence of base materials, spacer type and protein modification: J. Chromatogr. 1994, 677, 229-237)) for the reasons stated in numbered paragraph 13 of the Office Action.

Step (a) of independent Claims 1, 12 and 29 is limited to "the solid support being formed from a material selected from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate and nylon." Neither Abbott et al. nor Haginiaka et al. disclose a solid support as set forth in Claims 1, 12 and 29. In addition, neither Abbott et al. nor Haginiaka et al. teach or suggest forming an activated support, "wherein the activating compound is 1,2,4-carbonyl di-triazole" nor "reacting the biological molecule with the 1,2,4-carbonyl di-triazole activated support."

Accordingly, the combination of Abbott et al. and Haginiaka et al. fail to teach all the limitations of the claimed invention. Applicants request withdrawal of the Rejection under 35 U.S.C. § 103(a) on this basis.

**CONCLUSION**

The Applicant believes that all pending claims are in condition for allowance and such action is earnestly requested. If the present amendments and remarks do not place the Application in condition for allowance, the Examiner is encouraged to contact the undersigned directly if there are any issues that can be resolved by telephone with the Applicants representative.

If any extension of time is required for this response, such extension is hereby requested. The Commissioner is hereby authorized to charge payment of any fees associated with this communication, if such fees are due, to Deposit Account No. 19-2090.

Respectfully Submitted,

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